PATENT COOPERATION TREATY

02 NOV. 2004

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

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Date of mailing (day/month/year) 02 November 2004 (02.11.2004)	
Applicant's or agent's file reference C-392	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2004/006513	International filing date (day/month/year) 17 June 2004 (17.06.2004)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 20 June 2003 (20.06.2003)
Applicant ZAMBON GROUP SPA et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. (If applicable) An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
20 June 2003 (20.06.2003)	MI2003A001247	IT	20 Octo 2004 (20.10.2004)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C-392	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/EP2004/006513	International filing date *(day/month/year)* 17.06.2004	Priority date *(day/month/year)* 20.06.2003
International Patent Classification (IPC) or national classification and IPC C07C227/40, C07C227/42, C07C229/28		
Applicant ZAMBON GROUP SPA et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.01.2005	29.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2398- 8239. H. Lorenzo Valera.

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-4 as originally filed

   Claims, Numbers

   1-5 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-5
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	2-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 02/34709 A (NICOLI ANDREA ; ZAMBON SPA (IT); CANNATA VINCENZO (IT); CORCELLA FRANC) 2 May 2002 (2002-05-02)

D2: DYE S R ET AL: "EQUILIBRIUM SORPTION OF AMINO ACIDS BY A CATION-EXCHANGE RESIN" INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 29, no. 5, 1 May 1990 (1990-05-01), pages 849-857, XP000165650 ISSN: 0888-5885

D3: EP-A-0 414 263 (GOEDECKE AG) 27 February 1991 (1991-02-27)

D4: WO 00/01660 A (ARRIGHI KATIUSCIA ; PAIOCCHI MAURIZIO (IT); RUSSO LAURA (IT); VILLA MA) 13 January 2000 (2000-01-13)

1. The present application relates to a process for the preparation of gabapentin which comprises the passage of gabapentin inorganic salt through a strong cationic exchange resin, the elution of gabapentin fixed on the column, the concentration of the resultant solution and the crystallization from an organic solvent, characterized in that the elution of gabapentin fixed on the column is carried out by using ammonia and an alkaline hydroxide aqueous solution; NaOH is mentioned as one of the alkaline hydroxide used in the process.

2. D1 discloses a process for the preparation of gabapentin which comprises the passage of gabapentin inorganic salt through a strong cationic exchange resin, the elution of gabapentin fixed on the column, the concentration of the resultant solution and the crystallization from an organic solvent, characterized in that the elution of gabapentin fixed on the column is carried out by using an ammonia solution prepared from ammonia and water.

3. D2 discloses the separation of amino acids by using ion exchange resins (in particular strong acid cation exchange resins) (see the passages mentioned in the search report).

4. D3 and D4 disclose a process for the preparation of gabapentin which comprises the passage of gabapentin inorganic salt through a weak cationic ionic exchange resin, the elution of gabapentin fixed on the column, the concentration of the

resultant solution and the crystallization from an organic solvent (see the passages mentioned in the search report).

Novelty

5. The subject-matter of claim 1 is not novel in the sense of Art. 33(2) PCT.

D1 discloses a process for the preparation of gabapentin which comprises the passage of gabapentin inorganic salt through a strong cationic exchange resin, the elution of gabapentin fixed on the column, the concentration of the resultant solution and the crystallization from an organic solvent, characterized in that the elution of gabapentin fixed on the column is carried out by using an ammonia solution prepared from ammonia and water. Taking into account that a solution prepared from ammonia and water is a solution of ammonium hydroxide and the elution in claim 1 is carried out with an ammonia and an alkaline hydroxide aqueous solution (an alkaline hydroxide is any hydroxide due to the fact that alkaline is an adjective which means alkali and any single hydroxide is alkaline), the disclosure of D1 anticipates the subject-matter of claim 1, which is therefore not novel.

Inventive step

6. The subject-matter of claims 2-5 cannot be considered to involve an inventive step in the sense of Art. 33(3) PCT.

6.1. The closest state of the art, D1, discloses a process for the preparation of gabapentin differing from the present claimed process in the fact that ammonia and water, an ammonium hydroxide solution, is used in the elution of gabapentin.

6.2. The present claimed process differs from the process of D1 in the fact that an aqueous solution of NaOH is used in the process in combination with ammonia instead of using water in combination with ammonia as in D1.

6.3. In view of the fact that water has to be used as well in the process disclosed in the application after using the ammonia and NaOH aqueous solution in order to elute the cationic exchange resin, there is no beneficial effect in the fact of additionally using an aqueous sodium hydroxide solution. Hence, an inventive step cannot be

acknowledged.
Further comments

7. The terms "alkaline hydroxide" used in claim 1 as well as in the description lead to lack of clarity, contrary to Art. 6 PCT. This expression is not concise due to the fact that an aqueous solution of a hydroxide is always alkaline. Therefore, the terms "alkaline hydroxide aqueous solution" are not concise.

8. It is clear from the description and the examples that the features of a)using gabapentin hydrochloride as the gabapentin inorganic salt introduced in the strong cationic exchange resin, b)the specific strong cationic exchange resins used in the process and c)the specific hydroxide used in the process are essential to the definition of the invention. Depending on which inorganic salt of gabapentin used, different resins and eluents have to be used in order to obtain gabapentin with high purity and yield. Since independent claim 1 does not contain these features a), b) and c), it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

9. The use of the word "about", especially in connection with numerical ranges, is generally regarded as rendering the determination of the exact scope of the range difficult. When used in a claim as well as in the description, this results in lack of clarity, contrary to Art. 6 PCT. Therefore, claim 5 as well as the description need to be adequately redrafted by deletion of said word in each of its occurrences.

10. The term "substantially" used in the description is vague and does not have a generally accepted meaning in the art, leading therefore to lack of clarity, contrary to Art. 6 PCT.

11. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims.

12. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 19 (2) and 34(2) PCT, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.